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(e) a nucleotide sequence complementary to any of (a), (b), or (c).

REMARKS

Claims 1-61 are pending in this application. The Office has withdrawn claims 1-8, 11-14, 18-35, 44, 45, and 50-61 from consideration. The Office has rejected claims 9, 10, 15-17, 36-43, and 46-49. Certain paragraphs of the specification have been amended to correct clerical and/or typographical errors. Changes to the amended paragraphs are shown in the attached Appendix.

Applicants have amended claims 9, 10, and 16 to incorporate the limitations of the nonelected claims from which they originally depended. Applicants also have corrected the mistake in claim 15 as suggested by the Office. The change is supported by the specification, for example, at page 5, lines 14-16. In addition, Applicants have amended claims 9, 10, 15, and 16 to recite an "apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment," which the specification defines as:

> a polypeptide that has a truncation at the amino terminus (with or without a leader sequence) and/or a truncation at the carboxy terminus of an AFTI polypeptide described herein, AFTI polypeptide allelic variants, AFTI polypeptide orthologs, AFTI polypeptide splice variants and/or an AFTI polypeptide variant having one or more amino acid additions or substitutions or internal deletions (wherein the resulting polypeptide is at least 6 amino acids in length) as compared to an AFTI polypeptide amino acid sequence specifically described herein.

The amendments to claims 9, 10, 15, and 16 are shown in the attached Appendix.

Objections to the Claims

The Office has objected to claims 9, 10, and 16 for their dependence from nonelected claims 7, 8, and 2, respectively. (Office Action, page 2.) The Office also

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has objected to claim 15 for its recitation of "75 to 113" rather than "73 to 113." (*Id.*, page 3.)

Based on the above claim amendments, Applicants respectfully request the withdrawal of the objections to claims 9, 10, 15, and 16.

Objection to the Specification

The Office has objected to the specification as allegedly failing to provide proper antecedent basis for the recitation of "polypeptide consisting essentially of" in claim 15. (*Id.*, pages 2-3.)

Applicants note that the specification recites the precise language of claim 15. *See* Specification, page 4, lines 27-28 ("In certain other embodiments, the invention relates to *an isolated polypeptide* ***consisting essentially of*** *an amino acid sequence selected from* . . ."). Applicants respectfully request the withdrawal of the objection to claim 15.

The Claims Are Enabled

The Office has rejected claims 9, 10, 15-17, 36-43, and 46-49 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. (*Id.* pages 3-6.) According to the Office, the specification does not enable one skilled in the art "to make and use the invention commensurate in scope with these claims." (*Id.*, page 6.) The Office reaches this conclusion by applying some, but not all, of the factors from *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). According to the Office, "[t]he factors most relevant to this rejection are the scope of the claim, the amount of direction and guidance provided, the lack of sufficient working examples, the unpredictability of the art, and the amount of experimentation required." (Office Action, page 6.)

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Applicants respectfully traverse. To satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, a patent application must adequately disclose the claimed invention so as to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 52 U.S.P.Q.2d 1129, 1136 (Fed. Cir. 1999).

Applicants submit that the Office has not met its initial burden to establish a reasonable basis to question enablement. M.P.E.P. § 2164.04 (citing *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)).

> [A] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for the enabling support.

In re Marzocchi, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) (emphasis in original); *see also* M.P.E.P. § 2164.04.

The "invention" that must be enabled is that defined by the particular claim or claims of the patent or patent application. *See* M.P.E.P. § 2164; *see also Phillips Petroleum Co. v. U.S. Steel Corp.*, 673 F. Supp. 1278, 6 U.S.P.Q.2d 1065 (D. Del. 1987), aff'd, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989). Here, the rejected claims recite apo-A-I fragment T-cell activation inhibitor-like ("AFTI") polypeptide fragments that are encoded by particular nucleic acid sequences, AFTI polypeptide fragments covalently modified with water-soluble polymers, AFTI polypeptide fragment fusion proteins, and compositions comprising AFTI polypeptide fragments.

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As an initial matter, Applicants note that the *Wands* factors not considered "relevant" by the Office (the nature of the invention; the state of the prior art; and the relative skill of those in the art) favor a finding that the pending claims *are* enabled. According to M.P.E.P. § 2164.01(a), "[t]he examiner's analysis must consider all the evidence related to each of [the *Wands*] factors, and any conclusion of nonenablement must be based on the evidence as a whole."

The properties of apo A-I were well known at the time the earliest priority document was filed, March 13, 2000. In fact, a search of the PubMed database by Applicants' representative showed that nearly 5000 scientific papers concerning apo A-I had been published before that date. In addition, a search of the Genbank database for "apolipoprotein A-I" returned 452 protein and 1484 nucleotide sequences from a wide variety of species. Moreover, artisans in this area are highly skilled and often have doctoral degrees. This evidence, none of which the Office appears to have considered, favors the conclusion that claims 9, 10, 15-17, 36-43, and 46-49 are enabled.

The Office asserts, however, that the rejected claims are not enabled because, *inter alia*, they are unduly broad. (Office Action, pages 6-11.) According to the Office, the transitional phrase "consisting essentially of" is open-ended and claims 9, 10, 15-17, 36-43, and 46-49 therefore encompass an "indefinite number of undisclosed polypeptide[s] and the corresponding nucleotides for the additional amino acids." (*Id.*, page 7.) But this is incorrect.

The phrase "'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention." M.P.E.P. § 2111.03 (citing *In re Herz*, 537

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F.2d 549, 551-52 (C.C.P.A. 1976)) (emphasis in original); *see also Regents of the Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1573 (Fed. Cir. 1997) (noting that the Examiner was correct in interpreting a claim reciting "human [proinsulin] ***consisting essentially of*** a plus strand having the sequence [nucleotides that encode human proinsulin]" to exclude fusion proteins) (emphasis in original).

Moreover, the specification makes it clear that the phrase "consisting essentially of" is not open-ended like the phrase "comprising." In fact, Applicants have distinguished between two embodiments of their invention: 1) "an isolated polypeptide consisting essentially of an amino acid sequence selected from . . ." (e.g., page 4, line 27, to page 5, line 13) and 2) "an isolated polypeptide comprising the amino acid sequence selected from . . ." (e.g., page 5, line 24, to page 6, line 15). Therefore, claims 9, 10, 15-17, 36-43, and 46-49 do not encompass an "indefinite number" of polypeptides and nucleic acids, as asserted by the Office. Instead, those claims encompass only sequences in addition to the recited fragments of SEQ ID NOs: 1 and 2 that do not "materially affect the basic and novel characteristic(s)" of the claimed AFTI polypeptide fragments.

The Office also alleges that claims 9, 10, 15-17, 36-43, and 46-49 are not enabled because the specification does not provide sufficient guidance or working examples. First, the Office asserts that "there is insufficient guidance as to the specific amino acids [that] should be added and whether the resulting polypeptide after modification will still retain the structural and functional properties of SEQ ID NO:2, in turn, for pharmaceutical use." (Office Action, page 7.)

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As an initial matter, the claims do not require that *any* amino acids *should* be added to the AFTI polypeptide fragments. Instead, the claims recite particular AFTI polypeptide fragments (and homologous sequences) which may also contain additional amino acids so long as those amino acids do not "materially affect the basic and novel characteristic(s)" of the claimed polypeptides. In view of the breadth of knowledge concerning apo A-I structure and function, the Office has provided no reason to conclude that one skilled in the art would encounter any difficulty in determining what amino acids might be added to specific AFTI polypeptide fragments without materially modifying their properties.

Moreover, none of the rejected claims specifically recites a pharmaceutical use. Where a product claim does not recite a specific use, "if *any use* is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. § 2164.01(c) (emphasis added). Claims 9, 10, 15-17, 36-43, and 46-49 recite AFTI polypeptide fragments, AFTI polypeptide fragments covalently modified with water-soluble polymers, AFTI polypeptide fragment fusion proteins, and compositions comprising these polypeptides. The specification discloses multiple uses of AFTI polypeptide fragments, including, for example, use as antigens. (Page 15, lines 12-15.)

The Office has improperly rejected these claims because the specification allegedly does not enable methods of treating disease (Office Action, page 7). That the compositions of claims 36-39 also comprise a pharmaceutically acceptable carrier does not require that they be enabled for use in treating a disease. Claims 36-39 simply recite "compositions." They do not recite "pharmaceutical compositions."

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The Office next asserts that the specification does not provide sufficient guidance to enable one skilled in the art to make and use AFTI polypeptide fragments from nucleic acids that hybridize to SEQ ID NO:1 under moderately or highly stringent conditions. (Office Action, pages 7-8.) According to the Office, "the specification does not disclose the specific conditions used by applicants such as salt concentration, melting and annealing temperature and the duration of hybridization for the specific polynucleotide encoding the specific polypeptide." (*Id.*, page 8.) The Office states that "determining the specificity of hybridization is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable." (*Id.*, emphasis in original)

Applicants respectfully direct the Office to pages 21-23 of the specification, which provide a detailed description of hybridization conditions that are "highly" or "moderately" stringent. The Office has provided no evidence that one skilled in the art would be forced to engage in undue experimentation in order to identify nucleic acids that hybridize to SEQ ID NO:1 under such conditions or to determine whether those nucleic acids encoded AFTI polypeptide fragments. Even if, as the Office asserts, some aspects of this process may be empirical or some oligonucleotides may not behave as predicted, that does not mean that Applicants' invention is not enabled. A significant amount of routine work is not the same as "undue experimentation." *See Wands*, 858 F.2d at 737 ("The key word is 'undue,' not 'experimentation.'").

The Office also reports that a database search for 20-mers of the "specified sequence" identified 143,797,728 "hits," suggesting "that *some* of the polynucleotides encompassed by the claims would not preferentially hybridize to SEQ ID NO:1." (Office Action, page 8, emphasis added.) Apparently, in the opinion of the Office, this supports

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a conclusion that the claims are not enabled for AFTI polypeptide fragments encoded by nucleic acids that hybridize under highly or moderately stringent conditions with the complements of the nucleotide sequences recited in (a) to (f) of claim 1.

With the information provided by the Office, Applicants cannot completely address this issue. The smallest nucleotide sequence encoding an AFTI polypeptide fragment according to claim 1(a) to (f) is 117 nucleotides long (residues 75 to 113 of SEQ ID NO:2). The Office fails to explain why a 20-mer is at all relevant to the claim. The Office also fails to explain what search parameters were used to retrieve the 143,797,728 "hits" or how this analysis relates to whether the specification enables one skilled in the art to make and use AFTI polypeptide fragments. The Office fails to indicate whether the "specified sequence" is the nucleic acid SEQ ID NO:1 or all sequences possibly encoding the protein SEQ ID NO:2 or some other sequence. Moreover, the Office fails to explain how its search results support a conclusion that "some of the polynucleotides encompassed by the claims would not preferentially hybridize to SEQ ID NO:1" or why this, even if true, is relevant to enablement.

In view of the vast amount of information publicly available regarding apo A-I protein and nucleotide sequences (see above), the Office cannot credibly assert that the claims are not enabled simply because *some* conditions can be imagined under which *some* false positive sequences *may* be identified. First, the claims require not only that a nucleic acid hybridize with the complement of a specific sequence, but also that they encode a polypeptide with an activity of SEQ ID NO:2. The Office has provided no evidence that one skilled in the art would have any difficulty making and using any of the sequences among the 143,797,728 "hits" that may satisfy these criteria. Even

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assuming, that the Office is correct, however, the inclusion within the claims of some inoperative embodiments does not render the claims not enabled. *See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) ("It is not a function of the claims to specifically exclude . . . possible inoperative substances").

The Office next asserts that, because the specification discloses only human apo A-I sequences, it does not provide sufficient guidance to enable one skilled in the art to make and use an AFTI polypeptide fragment from a nucleic acid that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to a nucleotide sequence of claim 1. (Office Action, page 8.) The Office makes similar assertions regarding allelic and splice variants of the apo A-I gene, as well as orthologs of the human apo A-I protein sequence and polypeptides that are 70 to 99 percent identical to SEQ ID NO:2. (*Id.*, pages 9-10.) Attempting to support these conclusions, the Office relies on Atwood for the proposition that "protein function is context-dependent." (*Id.*, page 8, 10.)

But, Applicants are not required to disclose that which is well known in the art. *See Wands*, 858 F.2d 735 ("A patent need not disclose what is well known in the art."). Here, 452 apo A-I protein sequences and 1484 apo A-I nucleotide sequences are immediately retrievable from an online database. (See above.) Applicants have provided examples of AFTI polypeptide fragments from one species. The Office has pointed to no evidence that one skilled in the art would have any difficulty identifying additional AFTI polypeptide fragments from known sequences or would require additional guidance in order to do so. Atwood, which addresses issues in bioinformatics, is totally inapposite to this question. Instead, Atwood discusses whether

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one can reliably predict the function of a protein based on the presence of regions with homology to known functional domains of other proteins. (*See* pages 2-3.)

Finally, the Office asserts that the specification does not enable one skilled in the art to make and use a polypeptide produced from a polynucleotide consisting essentially of a nucleotide sequence according to claim 2, wherein the polynucleotide comprises a fragment of at least 16 nucleotides or a polynucleotide encoding a polypeptide of at least 25 amino acid residues. (Office Action, page 9, 10-11.) According to the Office, the transitional term "comprising" renders the polynucleotide open-ended. (*Id.*) Moreover, the Office asserts that the specification provides insufficient guidance and working examples of such polynucleotides. (*Id.*)

Again, however, the claimed polypeptides are produced using nucleotide sequences *consisting essentially of* the sequences recited by claim. That the recited sequences *comprise* smaller sequences does not render them open-ended. The metes and bounds are still set by SEQ ID NOs:1 and 2 and those amino acids that do not "materially affect the basic and novel characteristic(s)" of the claimed polypeptides. The Office has pointed to no evidence that one skilled in the art would have any difficulty identifying such polynucleotides based on the many known apo A-I sequences or would require additional guidance in order to do so.

Based on the above, Applicants respectfully request the withdrawal of the rejection of claims 9, 10, 15-17, 36-43, and 46-49 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled.

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The Specification Supports the Claims

The Office has also rejected claims 9, 10, 15-17, 36-43, and 46-49 under 35 U.S.C. § 112, first paragraph, as allegedly not being described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action, page 11.) According to the Office, there is insufficient written description of any AFTI polypeptide fragment consisting essentially of any amino acid sequence recited by the claims. (*Id.*)

Applicants respectfully traverse. The Office bears the burden of "presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims." M.P.E.P. § 2163(II)(A). Here, where the claims in question are the original claims, "there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed." *Id.* (citing *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976)). "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." *Id.*, § 2163(I).

Here, Applicants have explicitly described three nucleic acid sequences (nucleotides 73 to 601, 73 to 451, and 485 to 820 in SEQ ID NO:1) and five amino acid sequences (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113, and 156 to 267 in SEQ ID NO:2) that encode or are AFTI polypeptide fragments according to the invention. In

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addition, Applicants have described in great detail hybridization conditions and preferred amino acid substitutions that identify homologous or related sequences that are also part of their invention. (Specification, pages 21-31.) Moreover, Applicants have described the functional properties of the claimed polypeptides. Given the extensive database of known apo A-I nucleotide and amino acid sequences, one of skill in the art, contrary to the Office's assertion, would certainly conclude that Applicants were in possession of a representative number of species to describe the genus. Despite its unfounded assertion that the claims encompass "any polypeptide" and "any nucleotide sequence," the Office has provided *no* evidence to meet its burden of "presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims."

For the foregoing reasons, Applicants respectfully request the reconsideration of the rejection of claims 9, 10, 15-17, 36-43, and 46-49 under 35 U.S.C. § 112, first paragraph, as allegedly not meeting the written description requirement.

Claim 15 Is Definite

The Office has rejected claim 15 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. (Office Action, page 14.) The Office states that the recitation of "wherein the encoded polypeptide" in claim 15(f) is ambiguous because only polynucleotides encode polypeptides. (*Id.*)

Applicants have amended claim 15 as suggested by the Office to delete the word "encoded" from part (f). Because the claim as-filed recited "an isolated polypeptide," this amendment does not change the scope of claim 15. Applicants respectfully request the withdrawal of the rejection of claim 15 under 35 U.S.C. § 112, second paragraph.

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The Claims Are Not Anticipated

The Office has rejected claims 15 and 46 under U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,408,038 to Smith et al. ("the '038 patent"). (Office Action, page 15.) According to the Office, the '038 patent discloses various polypeptides that are fusions of apo A-I and apolipoprotein B (apo B). (*Id.*) Because Applicants' claims use the transitional term "consisting essentially of," the Office contends that they are anticipated by the '038 patent. (*Id.*)

Applicants respectfully traverse. In order to anticipate a claim, a prior art reference must teach every limitation of the claim. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986) ("It is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention, and that such a determination is one of fact."). Here, the Office again relies on the incorrect assertion that the transitional term "consisting essentially of" expands the claims to encompass the fusion proteins of the '038 patent. (Office Action, page 15.) Construing claims 15 and 46 in this way, however, adds subject matter that "materially affect[s] the basic and novel characteristic(s)" of the claimed polypeptides. The Office has provided no basis on which one could reasonably conclude that preparing fusion proteins comprising significant portions of both apo A-I and apo B does not materially affect the basic and novel characteristics of Applicants' AFTI polypeptide fragments. Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 15 and 46 under § 102(b) in view of the '038 patent.

The Office has rejected claims 10, 15-17, 46, and 48 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,721,114 to Abrahamsén et al. ("the

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'114 patent"). According to the Office, the '114 patent discloses (i) the Apo A-I Milano protein, (ii) a carboxy terminal fragment of the Apo A-I Milano protein that is at least 25 amino acids long and consists of amino acids 185-243, and (iii) a fusion protein between apo A-I and either β-galactosidase or the IgG binding domain of protein A. (Office Action, pages 15-16.)

Applicants respectfully traverse. The rejected claims recite apo-A-I fragment T-cell activation inhibitor-like ("AFTI") polypeptide fragments that are encoded by particular nucleic acid sequences and AFTI fragment fusion proteins. The disclosure of the Apo A-I Milano protein, which is not a fragment of apo A-I, cannot anticipate these claims. Likewise, the disclosure of a fusion protein containing the entire apo A-I protein cannot anticipate the fusion protein according to the instant claims, which contains a *fragment* of apo A-I. The Office cannot properly expand claims 10, 15-17, 46, and 48, which use the transitional phrase "consisting essentially of," to encompass the intact apo A-I proteins it asserts are disclosed by the '114 patent. To do so would "materially affect the basic and novel characteristic(s)" of the claimed AFTI polypeptide fragments.

In addition, although the '114 patent does disclose a carboxy terminal fragment of the Apo A-I Milano protein that is at least 25 amino acids long and consists of amino acids 185-243, the patent provides no support for the Office's conclusion that this peptide "has an activity of the polypeptide as set forth in SEQ ID NO:2" as required by claims 10(m), 15(h), 16(c), 17, 46, and 48. One skilled in the art would not reasonably believe that the peptide described in the '114 patent had *any* activity since it was prepared using methods widely known to inactivate proteins: incubation for a prolonged

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period (5 h) at elevated temperature (40°C) and pH (9.4) in a denaturing medium followed by reverse-phase HPLC (col. 10, line 63, to col. 11, line 8).

Moreover, the '114 patent does not anticipate the fusion proteins of claims 46 and 48. With regard to fusion proteins, the '114 patent states only:

> Attempts have been made to produce human Apo AI by way of recombinant DNA technology. In the European patent publication No. 0267703 the preparation of Apo AI from *E. coli* is described. The process describes a chimeric polypeptide where the Apo AI moiety is fused to the N-terminal amino acid residues of β-galactosidase or to one or more IgG-binding domains of Protein A, or to the prosequence of human Apo AI.

Col. 2, lines 6-13.

This is certainly not an anticipation of claims 46 and 48, which recite fusion proteins comprising AFTI polypeptide fragments, not fusion proteins comprising the complete apo A-I protein. Moreover, this is hardly a disclosure that would enable one skilled in the art to make or use any fusion proteins comprising apo A-I. Rather, the '114 patent appears to describes *failed* attempts to make recombinant apo A-I in bacteria.

Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 10, 15-17, 46, and 48 under 35 U.S.C. § 102(b) as allegedly being anticipated by the '114 patent.

The Office has rejected claims 9, 10, 15-17, and 36 under 35 U.S.C. § 102(b) and under 35 U.S.C. § 102(e) as allegedly being anticipated by PCT publication number WO 96/37608 and U.S. Patent No. 6,258,596, respectively, both to Benoit et al. ("the Benoit references"). (Office Action, pages 16-17.) Although the Office addresses these

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references separately, the U.S. Patent issued from the national phase of the PCT application. Applicants will therefore address the two rejections together.

Again, the Office ignores the meaning of "consisting essentially of" in rejecting claims 9, 10, 15-17, and 36 over the Benoit references. Those references discuss purified apo A-I and various purified apo A-I mutants. Like the '114 patent, these are not the AFTI polypeptide fragments recited by claims 9, 10, 15-17, and 36. Because the instant claims are limited to the recited AFTI polypeptide fragments and variations that do not "materially affect the basic and novel characteristic(s)" of the AFTI polypeptides, claims 9, 10, 15-17, and 36 are not anticipated by the Benoit references.

Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 9, 10, 15-17, and 36 under 35 U.S.C. §§ 102(b) and 102(e) as allegedly being anticipated by the Benoit references.

The Claims Are Not Obvious

The Office has also rejected various subsets of the claims under 35 U.S.C. § 103(a) as allegedly being obvious over six combinations of references, as follows:

1. claims 15, 46, and 47 over the '038 patent in view of U.S. Patent No. 5,116,964 ("the '964 patent");

2. claims 15, 16, and 46-49 over the '114 patent in view of the '964 patent;

3. claims 15, 16, and 46-49 over the Benoit references in view of the '964 patent;

4. claims 15, 36, 38, 40, and 41 over the '038 patent in view of U.S. Patent No. 5,824,784 ("the '784 patent");

5. claims 15, 16, and 36-43 over the '114 patent in view of the '784 patent; and

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6. claims 15, 16, and 36-43 over the Benoit references in view of the '784 patent. (Office Action, pages 17-24.)

In making each of these rejections, the Office relies on the '038 patent, the '114 patent, and the Benoit references as discussed above. The Office acknowledges that these references do not disclose a "fusion polypeptide comprising a heterologous amino acid sequence." (*Id.*, pages 17-19.) According to the Office, the '964 patent teaches fusion proteins comprising the CH2 and CH3 constant domains of immunoglobulins and, therefore, supplies the missing element. (*Id.*, pages 17-20.) The Office also acknowledges that these references do not disclose either 1) a composition wherein the formulation agent comprises at least one of a carrier, adjuvant, solubilizer, stabilizer, or antioxidant or 2) modification of a polypeptide by a water-soluble polymer. (*Id.*, pages 20-23.) According to the Office, the '784 patent teaches these elements and, therefore, renders the claims obvious. (*Id.*, pages 20-24.)

Applicants respectfully traverse. For the reasons provided above, neither the '038 patent nor the '114 patent nor the Benoit references disclose any polypeptide or nucleic acid encompassed by the rejected claims. The addition of either the '964 patent or the '784 patent does not correct this deficiency, regardless of what those references teach concerning fusion proteins or water-soluble polymers. The Office has failed to make a *prima facie* case of obviousness and should withdraw its rejections of claims 15, 16, 36-43 and 46-49 under 35 U.S.C. § 103(a).

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SUMMARY

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: April 16, 2003

By: _____
William L. Strauss
Reg. No. 47,114

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APPENDIX TO AMENDMENT OF JANUARY 22, 2003

Version with Markings to Show Changes Made

Amendments to the Specification

Paragraph at line 2 on page 5:

--(e) an amino acid sequence as set forth in residues [75] 73 to 113 of SEQ ID NO:2;--

Paragraph beginning at line 8 on page 11:

--Figure 5: Presence of the inhibitory activity in protein fractions of HDL. HS was fractionated by high density centrifugation and the inhibitory activity of HDL and serum protein fractions was analyzed. Isolated HDL were further subjected to either delipidation (delipidated HDL) or proteolytic digestion with proteinase K (Proteinase K treated HDL). The inhibitory activity of fractions was compared to HS (whole serum). The final protein concentration for whole serum and serum proteins was 7 mg/ml ([black] stippled columns), 3.5 mg/ml ([gray] hatched columns), and 0.7 mg/ml (white columns). The final protein concentration for HDL and delipidated HDL was 0.2 mg/ml ([black] stippled columns), 0.1 mg/ml ([gray] hatched columns), and 0.02 mg/ml (white columns). The amount of proteinase K-treated HDL was estimated according to the protein concentration before proteolysis and was similar to untreated HDL. Results represent the percentage of IL-1β (Fig. 5B) or TNFα (Fig. 5A) production in the absence of inhibitor (mean .+-.SD, n=3).--

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Paragraph beginning at line 23 on page 11:

--Figure 6: Analysis of HDL binding to cells. (A) Inhibition of T cell-signalling by binding of HDL to membranes of stimulated HUT-78 cells; either membranes of stimulated HUT-78 cells (white columns), THP-1 cells (hatched columns), or both ([black] stippled columns) were preincubated in the absence (-) or presence of FCS (10%), HS (10%) or HDL (0.32 mg/ml protein) for 45 minutes on ice; after washing, treated (hatched and [black] stippled columns) and untreated (white columns) THP-1 cells were cultured in the presence of treated (white and [black] stippled columns) or untreated (hatched columns) membranes of stimulated HUT-78 cells; TNFα and IL-1β production was measured in 48 hours-culture supernatants. Results are expressed as percentage considering the production measured in the absence of inhibitor as 100%, mean .+-.SD, n=6. (B-F) Binding of unconjugated FITC and FITC-HDL (0.1 mg/ml) was assessed by flow cytometry on THP-1 cells (B), isolated human monocytes (C), unstimulated HUT-78 cells (D) and stimulated HUT-78 cells (E). FITC was used as a negative control. (F) Binding of FITC-HDL (10 .mu.g/ml) to stimulated HUT-78 cells in the presence or absence of purified anti-apo-A-I antibodies (100 .mu.g/ml) (ATCC, Manassas, Va.; catalogue number HB-9570).--

Paragraph beginning at line 16 on page 13:

--Figure 9: Apo A-I inhibits TNF.alpha. and IL-1.beta. in PBMC stimulated [bu] by either PHA or Tetanus Toxoid (TT). PBMC 4 X 10^5 cells/200 µl/well were stimulated by 1 µg/ml PHA (A and B) or by 10 µg/ml TT (C and D) in the presence of the indicated doses of apo A-I and HDL.--

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Amendments to the Claims

9. (Amended) [A] An apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment produced by [the] a process [of claim 7] comprising culturing a eukaryotic cell comprising a vector comprising a nucleic acid molecule consisting essentially of a nucleotide sequence selected from:

(a) the nucleotide sequence as set forth in residues 73 to 601 in SEQ ID NO:1;

(b) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO:2;

(c) the nucleotide sequence as set forth in residues 73 to 451 in SEQ ID NO:1;

(d) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO:2;

(e) the nucleotide sequence as set forth in residues 485 to 820 in SEQ ID NO:1;

(f) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO:2;

(g) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO:2;

(h) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO:2;

(i) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of at least one of (a) to (h), wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2;

(j) a nucleotide sequence complementary to at least one of (a)-(h);

(k) a nucleotide sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to at least one of (a)-(j), wherein the nucleotide sequence

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encodes a polypeptide that has an activity of the polypeptide as set forth in SEQ ID NO:2;

(l) a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence according to at least one of (a)-(j), wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2;

(m) a nucleotide sequence selected from at least one of (k) and (l) encoding a polypeptide of at least about 25 amino acid residues, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2;

(n) a nucleotide sequence selected from at least one of (k), (l), and (m) comprising a fragment of at least about 16 nucleotides; and

(o) a nucleotide sequence complementary to any of (k), (l), or (m),

wherein a culture condition suitable for expressing the polypeptide is selected and the polypeptide is isolated from the culture.

10. (Amended) [A] An apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment produced by [the] a process [of claim 8] comprising culturing a prokaryotic cell comprising a vector comprising a nucleic acid molecule consisting essentially of a nucleotide sequence selected from:

(a) the nucleotide sequence as set forth in residues 73 to 601 in SEQ ID NO:1;

(b) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO:2;

(c) the nucleotide sequence as set forth in residues 73 to 451 in SEQ ID NO:1;

(d) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO:2;

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(e) the nucleotide sequence as set forth in residues 485 to 820 in SEQ ID NO:1;

(f) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO:2;

(g) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO:2;

(h) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO:2;

(i) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of at least one of (a) to (h), wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2;

(j) a nucleotide sequence complementary to at least one of (a)-(h);

(k) a nucleotide sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to at least one of (a)-(j), wherein the nucleotide sequence encodes a polypeptide that has an activity of the polypeptide as set forth in SEQ ID NO:2;

(l) a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence according to at least one of (a)-(j), wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2;

(m) a nucleotide sequence selected from at least one of (k) and (l) encoding a polypeptide of at least about 25 amino acid residues, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2;

(n) a nucleotide sequence selected from at least one of (k), (l), and (m) comprising a fragment of at least about 16 nucleotides; and

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(o) a nucleotide sequence complementary to any of (k), (l), or (m),

wherein a culture condition suitable for expressing the polypeptide is selected and the polypeptide is isolated from the culture.

15. (Amended) An isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment consisting essentially of an amino acid sequence selected from: (a) an amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO:2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO:2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO:2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO:2; (e) an amino acid sequence as set forth in residues [75] 73 to 113 of SEQ ID NO:2; (f) an amino acid sequence for an ortholog of SEQ ID NO:2, wherein the [encoded] polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2; (g) an amino acid sequence that is at least about 70, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to the amino acid sequence of at least one of (a), (b), or (c), wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2; (h) a fragment of the amino acid sequence set forth in at least one of (a), (b), (c), (d), or (e) comprising at least about 25 amino acid residues, wherein the polypeptide has an activity of a polypeptide as set forth in SEQ ID NO:2; (i) an amino acid sequence for an allelic variant or splice variant of at least one of (a)-(f) wherein the polypeptide has an activity of a polypeptide as set forth in SEQ ID NO:2.

16. (Amended) An isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment encoded by [the] a nucleic acid molecule [of claim 2] consisting essentially of a nucleotide sequence selected from:

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(a) a nucleotide sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to at least one nucleotide sequence selected from:

(1) the nucleotide sequence as set forth in residues 73 to 601 in SEQ ID NO:1;

(2) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO:2;

(3) the nucleotide sequence as set forth in residues 73 to 451 in SEQ ID NO:1;

(4) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO:2;

(5) the nucleotide sequence as set forth in residues 485 to 820 in SEQ ID NO:1;

(6) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO:2;

(7) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO:2;

(8) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO:2;

(9) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of at least one of (1) to (8),

wherein the nucleotide sequence encodes a polypeptide that has an activity of the polypeptide as set forth in SEQ ID NO:2;

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(b) a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence selected from at least one of:

(1) the nucleotide sequence as set forth in residues 73 to 601 in SEQ ID NO:1;

(2) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO:2;

(3) the nucleotide sequence as set forth in residues 73 to 451 in SEQ ID NO:1;

(4) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO:2;

(5) the nucleotide sequence as set forth in residues 485 to 820 in SEQ ID NO:1;

(6) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO:2;

(7) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO:2;

(8) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO:2;

(9) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of at least one of (1) to (8),

wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2;

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(c) a nucleotide sequence selected from at least one of (a) and (b) encoding a polypeptide of at least about 25 amino acid residues, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO:2;

(d) a nucleotide sequence selected from at least one of (a), (b), and (c) comprising a fragment of at least about 16 nucleotides; and

(e) a nucleotide sequence complementary to any of (a), (b), or (c).

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